3. Remarks

Applicants acknowledge that claims 15, 16, 23-25, 29, 36, and 38 are pending in the application with claims 15, 16, and 29 being in independent form. Claims 1-14, 17-22, 26-28, 30-35, and 37 have been cancelled. Applicants reserve the right to pursue the subject matter of the cancelled claims in other patent applications. Applicants will address the issues presented in the Advisory Action and the Final Office Action using the numbering system employed by the Examiner.

The Examiner did not enter Applicants' amendments filed March 7, 2005 because the amended claim language (*i.e.*, "hematopoietic stem cells, progenitor cells, or both") assertedly raised new issues requiring further consideration and the possibility of new matter.

Claims 15, 16, 29, and 38 have been amended to specify that the method may use hematopoietic stem cells, progenitor cells, or hematopoietic stem and progenitor cells. Support for the amendment may be found in the specification, for example, at page 2, lines 25-28, which states:

> It was surprisingly found that flt3-ligand can also potently stimulate the generation of downstream or intermediate cells such as myloied precursor cells, monocytic cells, macrophages, B cells, and dendritic cells from CD34+ **bone marrow progenitors and stem cells**. (emphasis added)

At page 3, lines 14-18:

> The invention also provides a method of generating large quantities of dendritic cells ex vivo. Following collection of the patient's CD34+ **hematopoietic progenitors and stem cells**, flt3-ligand can be used to expand such cells in vitro (also known as ex vivo expansion) and to drive such CD34+ cells to differentiate into dendritic cells of the lymphoid or myeloid lineage. (emphasis added)

Thus, the specification teaches that hematopoietic stem *and* progenitor cells can be used to generate dendritic cells using flt3-ligand. The specification also teaches that one may wish to use hematopoietic stem cells *or* hematopoietic progenitor cells to generate dendritic cells and describes the art around isolating such cells and their use in generating dendritic cells using flt3-ligand (page 8, line 20 to page 10, line 15). As such, Applicants respectfully submit that the specification provides sufficient written description to support the new claim language.

Item 5: *§103(a) and Joint Inventorship of Claims*

Applicants acknowledge the obligations under 37 CFR 1.56 and note that the pending claims are commonly owned by the joint inventors.

Item 6: §102(e)

Claims 29 and 36 stand rejected under 35 U.S.C. §102(e) as being anticipated by *Lyman et al.* (USPN 5,843,423). Applicants respectfully traverse in light of the amendments and the following remarks.

Applicants thank the Examiner for noting that the limitation of generating dendritic cells was not an explicit step in the body of the claim. In response, Applicants have amended claim 29 to read as follows:

> An *in vitro* method, comprising:
>
> (a) collecting hematopoietic stem cells, progenitor cells, or hematopoietic stem and progenitor cells;
>
> (b) contacting the cells with a growth factor or cytokine *in vitro*, wherein the growth factor or cytokine consists of flt3-ligand; and
>
> (c) driving the cells to differentiate into a dendritic cell population.

Thus, the novel step of driving the cells to differentiate into a dendritic cell population distinguishes the claimed invention over *Lyman*. *Lyman* only teaches the use of flt3-L for expanding hematopoietic stem and/or progenitor cells. Support for the amendments may be found in the specification, for example, at page 3, lines 14-18, where it states: "The invention also provides a method of generating large quantities of dendritic cells ex vivo. Following collection of the patient's CD34+ hematopoietic progenitors and stem cells, flt3-ligand can be used to expand such cells in vitro **and drive such CD34+ cells to differentiate into dendritic cells.**"

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir. 1990). The identical invention must be shown in as complete detail as is contained in the . . . claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989), *cert. denied*, 110 S.Ct. 154 (1989). The elements must be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

Lyman fails to satisfy the legal standard of anticipation under 35 U.S.C. §102(e) because it does not disclose the *identical steps arranged in the same order* as in amended claim 29.

At page 3 the Examiner states:

> "Given that the starting cell population in combination with flt3-L and GM-CSF in the prior art meets the starting cell population and cytokines/growth factors recited in instant claim 29(a); the claimed functional limitations would be inherent properties of the referenced methods to contact hematopoietic stem or progenitor cells with flt3-L and GM-CSF."

It appears the Examiner is suggesting that claim 29 is inherently anticipated by *Lyman* because the step of exposing hematopoietic stem and/or progenitor cells to flt3-L to cause the hematopoietic stem and/or progenitor cells to proliferate (as taught by *Lyman*) is the same step that will generate dendritic cells. In light of the amendments to claim 29, Applicants respectfully traverse.

The proper standard by which inherent anticipation is assessed is that "[o]ne must show that the undisclosed information was known to be present in the subject matter of the reference." *Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Research, 304 F.3d 1221 (Fed Cir 2002).* In addition, the *Rosco* Court stated that the "....**inherency question is not based on whether an inherent feature of a prior art reference inherently results in a claimed invention, but whether one of skill in the art would read a prior art reference as inherently disclosing an invention.**" *Rosco, Inc. v. Mirror Lite Co., 304 F.3d 1373 (Fed Cir 2002).*

According to the Examiner, the inherent feature that's missing from *Lyman* is the fact that continued exposure of hematopoietic stem/progenitor cells to flt3-ligand drives the cells to differentiate into dendritic cells. The Federal Circuit has made it clear that the "missing element" must meet three criteria:

> When the reference is silent about the asserted inherent characteristic, such gap may be filled with extrinsic evidence. Such evidence must make clear that the missing element is: (1) necessarily present in the thing described in the reference; (2) that it would be so recognized by persons of ordinary skill; and (3) proven by evidence within the prior art time frame *(Cont'l Can Co. v. Monsanto Co* 20 USPQ2d 1746, 948 F.2d 1264 (Fed Cir 1991)).

Thus, exposing hematopoietic stem/progenitor cells to flt3-ligand to drive the cells to differentiate into dendritic cells must (1) **necessarily occur** in the method described in *Lyman*; (2) that this attribute would be **recognized by persons of ordinary skill**; and (3) proven by **evidence within the prior art time frame.**

If one part of the three-prong test is not satisfied, then a *prima facie* case has not been established. Applicants note that the *prima facie* case fails on all three counts. First, dendritic cells must *necessarily* be created by contacting flt3-ligand to hematopoietic stem and/or progenitor cells. The courts have defined "necessarily" in the context of inherent anticipation as "Inherency, however, may not be established by *probabilities or possibilities*. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." (*In re Oelrich*, 666 F.2d 578; 212 USPQ 323, 1981 – emphasis added).

In this case, dendritic cells are not generated *each and every time* hematopoietic stem and/or progenitor cells are exposed to flt3-ligand. This is evidenced by differences in culture conditions described in *Lyman* (USPN 5,843,423) and the present specification. At column 26, lines 22-37, *Lyman* teaches a method for expanding hematopoietic stem and progenitor cells. The stem cells were cultured for 4 days (96 hours plus 24 hours with radioactive tag) and cultured an additional 2 days in the presence of flt3-ligand. This is an approximate culture time of 6 days for expanding hematopoietic stem and/or progenitor cells. In contrast, Example 1 of the present application (page 15) describes culture conditions for generating large numbers of dendritic cells. Example 1 describes culturing CD34+ cells in the presence of flt3-ligand for approximately *2 weeks* (line 10). As taught in the specification at page 3, line 14, the hematopoietic stem and/or progenitor cells must be exposed to flt3-ligand for an extended period in order to (a) expand the hematopoietic stem and/or progenitor cells and (b) drive the expanded cells to differentiate into dendritic cells, *inter alia*.

Therefore, if one were to culture hematopoietic stem and/or progenitor cells with flt3-ligand for a time period that was insufficient to permit the cells to expand and differentiate, one would not generate dendritic cells *every time*, which is the legal standard required. Therefore, the Lyman reference does not support a *prima facie* case of inherent anticipation.

The second and third prongs require one of skill in the art to recognize the inherent feature and to recognize it at the time of the application's earliest effective filing date. As the Examiner is aware, the *Lyman* patent is Applicants' patent on the discovery of flt3-ligand and its ability to expand hematopoietic stem and progenitor cells. Not until later did the inventors in the present application discover that flt3-ligand had the additional capacity to drive the expanded hematopoietic stem and progenitor cells into dendritic cells. Thus, as of the earliest effective filing date of the present invention (10/4/1995), one of skill in the art had no basis whatsoever for recognizing or predicting that flt3-ligand could drive hematopoietic stem and progenitor cells to differentiate into dendritic cells. As such, the second and third elements of the three-prong test have not been satisfied and as a result a *prima facie* case of inherent anticipation has not been established.

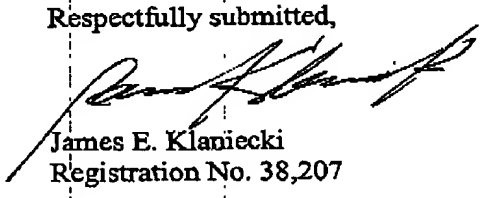
Item 7: §103(a)

Claims 29, 36 and 38 stand rejected under 35 U.S.C. §103(a) as being unpatentable over *Lyman, et al.* (USPN 5,843,423) in view of *Tsumamoto, et al.* (USPN 5,914,108). Applicants note that *Lyman, et al.* (USPN 5,843,423) only qualifies as prior art under §102(e).

The present application was filed on October 30, 2000, which entitles the present application to enjoy the benefit of revised 35 USC §103(c). This provision precludes the use of commonly owned subject matter as prior art under §103(a)/§102(e) (see, MPEP 706.02(l)(1) at 700-50). In support of Applicants' claim of common ownership between the present application and *Lyman, et al.* (USPN 5,843,423), a Statement by Applicants' representative of record is included with this response (see, MPEP 706.02(l)(2)(II) at 700-53, *et seq*). Because the primary reference has been disqualified, the rejection under §103(a)/§102(e) may be properly removed.

Applicants respectfully request reconsideration of the pending claims in light of the amendments and arguments presented above. If the Examiner believes that any issues could be resolved, or if the prosecution of the application could be expedited, by a telephone conference, Applicants invite the Examiner to telephone the undersigned at (206) 265-7145.

Respectfully submitted,



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